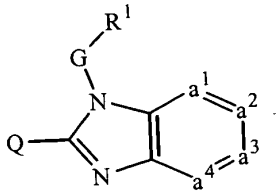
DOCKET NO.: JANS-0026 (JAB-1499 US)
Application No.: 10/019,380
Office Action Dated: July 14, 2003

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. ***(currently amended)*** A compound of formula



(I)

a prodrug, ~~**N-oxide,**~~ addition salt, ~~**quaternary amine, metal complex**~~ or stereochemically isomeric form thereof wherein

$-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula

-CH=CH-CH=CH- (a-1);

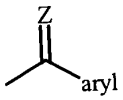
~~**-N=CH-CH=CH- (a-2);**~~

~~**-CH=N-CH=CH- (a-3);**~~

~~**-CH=CH-N=CH- (a-4); or**~~

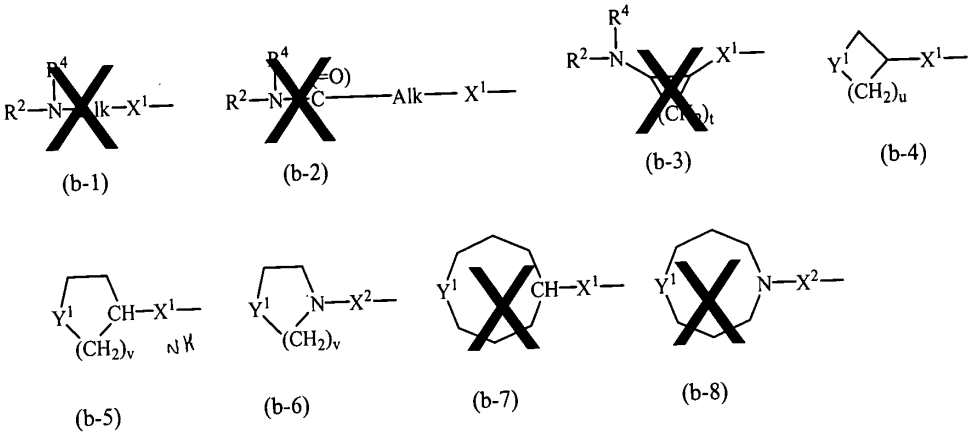
~~**-CH=CH-CH=N- (a-5);**~~

wherein each hydrogen atom in the ~~**radicals**~~ **radical** (a-1)~~**, (a-2), (a-3), (a-4) and (a-5)**~~ may optionally be replaced by halo, C_{1-6}alkyl, nitro, amino, hydroxy, C_{1-6}alkyloxy, polyhaloC_{1-6}alkyl, carboxyl, aminoC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, hydroxyC_{1-6}alkyl, or a radical of formula



wherein ~~**=Z**~~ **Z** is ~~**=O, =CH-C(=O)-NR^{5a}R^{5b}, =CH$_2$, =CH-C$_{1-6}$alkyl, =N-OH or =N-O-C$_{1-6}$alkyl**~~ **O, CH-C(=O)-NR^{5a}R^{5b}, CH$_2$, CH-C$_{1-6}$alkyl, N-OH or N-O-C$_{1-6}$alkyl**;

Q is a radical of formula



(b-1) (b-2) (b-3) (b-4)

(b-5) (b-6) (b-7) (b-8)

wherein ~~Alk is C_{1-6}alkanediyl~~;

Y^1 is a bivalent radical of formula $-NR^2-$ or $-CH(NR^2R^4)-$;

X^1 is NR^4, S, S(=O), $S(=O)_2$, O, CH_2, C(=O), $C(=CH_2)$, CH(OH), $CH(CH_3)$, $CH(OCH_3)$, $CH(SCH_3)$, $CH(NR^{5a}R^{5b})$, CH_2-NR^4 or NR^4-CH_2;

X^2 is a direct bond, CH_2, C(=O), NR^4, C_{1-4}alkyl-NR^4, NR^4-C_{1-4}alkyl;

~~t is 2, 3, 4 or 5;~~

u is ~~1, 2, 3, 4 or 5~~ **2 or 3;**

v is 2 ~~or 3~~; and

whereby each hydrogen atom in ~~Alk and~~ the carbocycles and the heterocycles defined in radicals ~~(b-3),~~ (b-4), (b-5), **and** (b-6)~~, (b-7) and (b-8)~~ may optionally be replaced by R^3; with the proviso that when R^3 is hydroxy or C_{1-6}alkyloxy, then R^3 can not replace a hydrogen atom in the α position relative to a nitrogen atom;

G is C_{1-10}alkanediyl substituted with one or more hydroxy, C_{1-6}alkyloxy, arylC_{1-6}alkyloxy, C_{1-6}alkylthio, arylC_{1-6}alkylthio, $HO(-CH_2-CH_2-O)_n-$, C_{1-6}alkyloxy $(-CH_2-CH_2-O)_n-$ or arylC_{1-6}alkyloxy$(-CH_2-CH_2-O)_n-$;

R^1 is a monocyclic heterocycle or aryl; said heterocycle being selected from piperidinyl, piperazinyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, tetrahydrofuranyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, isothiazolyl, pyrazolyl, isoxazolyl, oxadiazolyl; and each heterocycle may optionally be substituted with 1 or where possible more substituents selected from halo, hydroxy, amino, cyano, carboxy, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkyloxyC_{1-6}alkyl, aryl,

arylC$_{1-6}$alkyl, arylC$_{1-6}$alkyloxy, hydroxyC$_{1-6}$alkyl, mono-or di(C$_{1-6}$alkyl)amino, mono- or di(C$_{1-6}$alkyl)aminoC$_{1-6}$alkyl, polyhaloC$_{1-6}$alkyl, C$_{1-6}$alkylcarbonylamino, C$_{1-6}$alkyl-SO$_2$-NR^{5c}-, aryl-SO$_2$-NR^{5c}-, C$_{1-6}$alkyloxycarbonyl, -C(=O)-NR^{5c}R^{5d}, HO(-CH$_2$-CH$_2$-O)$_n$-, halo(-CH$_2$-CH$_2$-O)$_n$-, C$_{1-6}$alkyloxy(-CH$_2$-CH$_2$-O)$_n$-, arylC$_{1-6}$alkyloxy(-CH$_2$-CH$_2$-O)$_n$- and mono- or di(C$_{1-6}$alkyl)amino(-CH$_2$-CH$_2$-O)$_n$;

each n independently is 1, 2, 3 or 4;

R^2 is hydrogen, formyl, C$_{1-6}$alkylcarbonyl, Hetcarbonyl, pyrrolidinyl, piperidinyl, homopiperidinyl, C$_{3-7}$cycloalkyl substituted with N(R^6)$_2$, or C$_{1-10}$alkyl substituted with N(R^6)$_2$ and optionally with a second, third or fourth substituent selected from amino, hydroxy, C$_{3-7}$cycloalkyl, C$_{2-5}$alkanediyl, piperidinyl, mono-or di(C$_{1-6}$alkyl)amino, C$_{1-6}$alkyloxycarbonylamino, aryl and aryloxy;

R^3 is hydrogen, hydroxy, C$_{1-6}$alkyl, C$_{1-6}$alkyloxy, arylC$_{1-6}$alkyl or arylC$_{1-6}$alkyloxy;

R^4 is hydrogen, C$_{1-6}$alkyl or arylC$_{1-6}$alkyl;

R^{5a}, R^{5b}, R^{5c} and R^{5d} each independently are hydrogen or C$_{1-6}$alkyl; or

R^{5a} and R^{5b}, or R^{5c} and R^{5d} taken together form a bivalent radical of formula -(CH$_2$)$_s$- wherein s is 4 or 5;

R^6 is hydrogen, C$_{1-4}$alkyl, formyl, hydroxyC$_{1-6}$alkyl, C$_{1-6}$alkylcarbonyl or C$_{1-6}$alkyloxycarbonyl;

aryl is phenyl or phenyl substituted with 1 or more substituents selected from halo, hydroxy, C$_{1-6}$alkyl, hydroxyC$_{1-6}$alkyl, polyhaloC$_{1-6}$alkyl, and C$_{1-6}$alkyloxy; and

Het is pyridyl, pyrimidinyl, pyrazinyl, or pyridazinyl.

2. ***(cancelled)***

3. ***(previously presented)*** A compound according to claim 1, wherein R^1 is phenyl optionally substituted with halo, C$_{1-6}$alkyl or C$_{1-4}$alkyloxy; or pyridyl optionally substituted with 1 or more substituents selected from arylC$_{1-6}$alkyloxy,

C_{1-6}alkyloxyC_{1-6}alkyl, aryl, mono-or di(C_{1-6}alkyl)amino, C(=O)-$NR^{5c}R^{5d}$, halo or C_{1-6}alkyl.

4. ***(previously presented)*** A compound according to claim 1, wherein G is C_{1-4}alkanediyl substituted with hydroxy, C_{1-6}alkyloxy, $HO(-CH_2-CH_2-O)_n-$, C_{1-6}alkyloxy$(-CH_2-CH_2-O)_n-$ or arylC_{1-6}alkyloxy$(-CH_2-CH_2-O)_n-$.

5. ***(previously presented)*** A compound according to claim 1, wherein Q is a radical of formula (b-5) wherein v is 2 and Y^1 is $-NR^2-$.

6. ***(previously presented)*** A compound according to claim 1, wherein X^1 is NH or CH_2.

7. ***(previously presented)*** A compound according to claim 1, wherein R^2 is hydrogen or C_{1-10}alkyl substituted with NHR^6 wherein R^6 is hydrogen or C_{1-6}alkyloxycarbonyl.

8. ***(currently amended)*** A compound according to claim 1, wherein the compound is

[(A),(S)]-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(6-bromo-2-pyridinyl)ethoxymethyl]-1H-benzimidazol-2-amine;

[(A),(S)]-N-[1-(2-aminopropyl)-4-piperidinyl]-1-[ethoxy(6-methyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine ~~**(compound 75)**~~;

(±)-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(2-methoxyethoxy)(6-methyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine;

N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-6-chloro-1-[(2-methoxyethoxy)(6-methyl-2-pyridinyl)methyl]-4-methyl-1H-benzimidazol-2-amine trihydrochloride trihydrate;

[(A),(R)]-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[ethoxy(6-methyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine monohydrate;

(±)-N-[1-(2-aminopropyl)-4-piperidinyl]-1-[ethoxy(6-methyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine;

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[(A)(S)]-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[ethoxy(6-methyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine monohydrate;

(±)-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[ethoxy(6-methyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine;

[(A),(R)]-N-[1-(2-aminopropyl)-4-piperidinyl]-1-[ethoxy(6-methyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine monohydrate;

(±)-N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(6-bromo-2-pyridinyl)ethoxymethyl]-2-benzimidazol-2-amine;

(±)-N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-ethoxyethoxy)(6-methyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine;

[(B),(S)]N-[1-(2-aminopropyl)-4-piperidinyl]-1-[ethoxy(6-methyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine monohydrate;

(±)-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-3-[(2-methoxyethoxy)(6-methyl-2-pyridinyl)methyl]-7-methyl-3H-imidazo[4,5-b]pyridin-2-amine;

(±)-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(2-ethoxyethoxy)(6-phenyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine;

(±)-N-[1-(2-aminoethyl)-4-piperidinyl]-1-[(2-methoxyethoxy)(6-metyl-2-pyridinyl)methyl]-1H-benzimidazol-2-amine;

(±)-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(6-bromo-2-pyridinyl)ethoxymethyl]-4-methyl-1H-benzimidazol-2-amine monohydrate;

[(A),(R)]-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(6-bromo-2-pyridinyl)ethoxymethyl]-1H-benzimidazol-2-amine;

(±)-N-[1-(2-amino-3-methylbutyl)-4-piperidinyl]-1-[(6-bromo-2-pyridinyl)ethoxymethyl]-1H-benzimidazol-2-amine;

a prodrug, ~~N-oxide,~~ addition salt, ~~quaternary amine, metal complex~~ or stereochemically isomeric form thereof.

9. ***(currently amended)*** A method of treating a **respiratory syncytial** viral infection, comprising the step of administering a therapeutically effective amount of a compound as claimed in any one of claims 1 to 8.

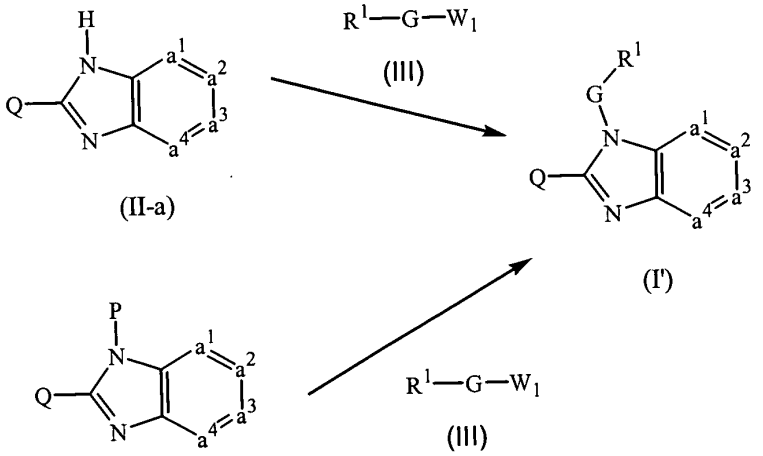
10. ***(previously presented)*** A pharmaceutical composition, comprising a pharmaceutically acceptable carrier, and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 8.

11. ***(previously presented)*** A process of preparing a composition as claimed in claim 10, comprising the step of intimately mixing said carrier with said compound.

Claims 12 to 14 ***(cancelled)***

15. ***(currently amended)*** A process of preparing a compound as claimed in claim 1, comprising at least one step selected from the group consisting of:

a) reacting an intermediate of formula (II-a) or (II-b) with an intermediate of formula (III)



with R^1, G, Q and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and W_1 being a leaving group, in the presence of a base and in a reaction-inert solvent;

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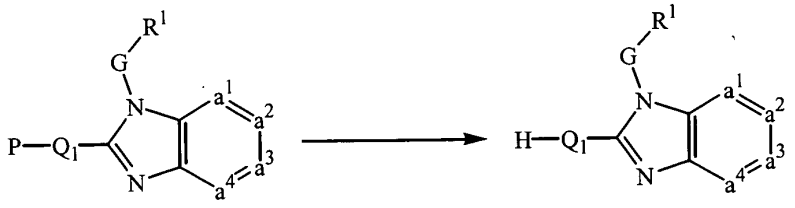
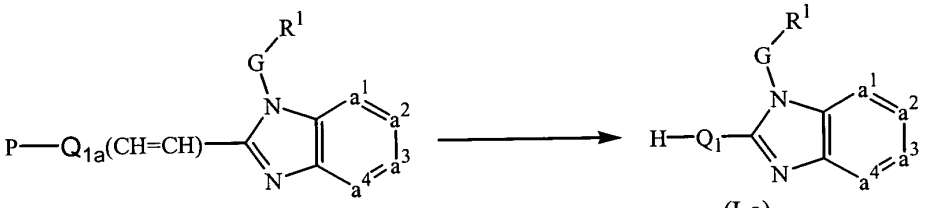
b) deprotecting an intermediate of formula (IV)



(IV) (I-a)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, H-Q_1 being defined as Q according to claim 1 provided that R^2 or at least one R^6 substituent is hydrogen, and P being a protective group;

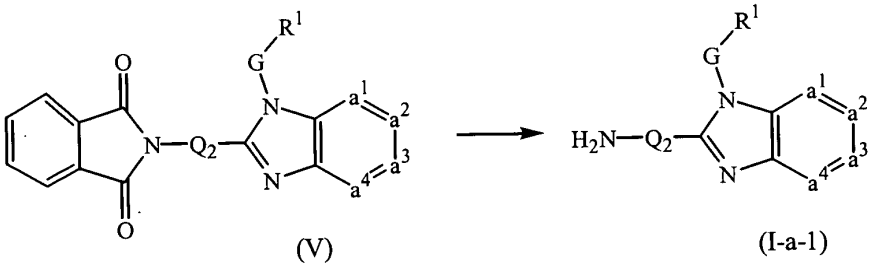
c) deprotecting and reducing an intermediate of formula (IV-a)



(IV-a) (I-a)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, H-Q_1 being defined as Q according to claim 1 provided that R^2 or at least one R^6 substituent is hydrogen, Q_{1a}(CH=CH) being defined as Q_1 provided that Q_1 comprises an unsaturated bond, and P being a protective group;

d) deprotecting an intermediate of formula (V)



(V) (I-a-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and H_2N-Q_2 being defined as Q according to claim 1 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen;

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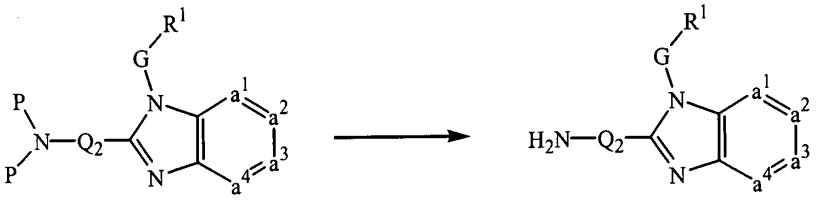
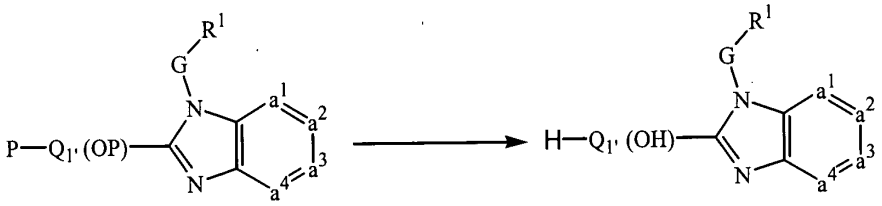
e) deprotecting an intermediate of formula (VI)



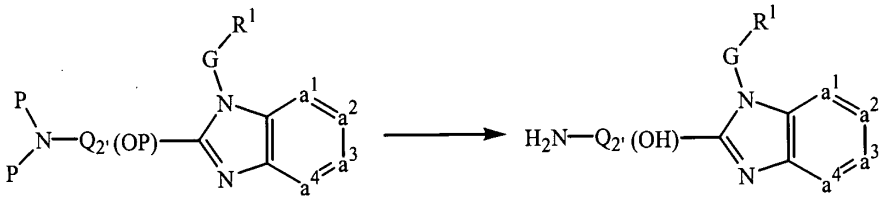
(VI) (I-a-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and H_2N-Q_2 being defined as Q according to claim 1 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen, and P being a protective group;

f) deprotecting an intermediate of formula (VII) or (VIII)



(VII) (I-a-2)



(VIII) (I-a-1-1)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, $H-Q_{1'}(OH)$ being defined as Q according to claim 1 provided that R^2 or at least one R^6 substituent is hydrogen and provided that Q comprises a hydroxy moiety, $H_2N-Q_{2'}(OH)$ being defined as Q according to claim 1 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen and provided that Q comprises a hydroxy moiety, and P being a protective group;

g) amination of an intermediate of formula (IX)

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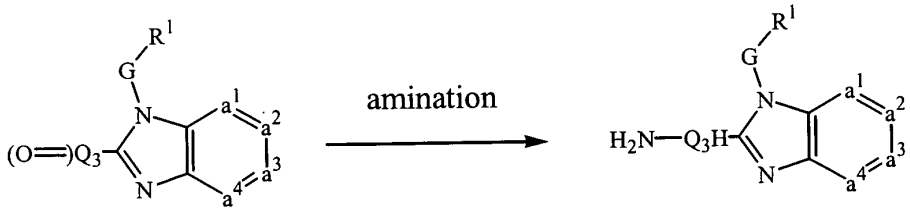
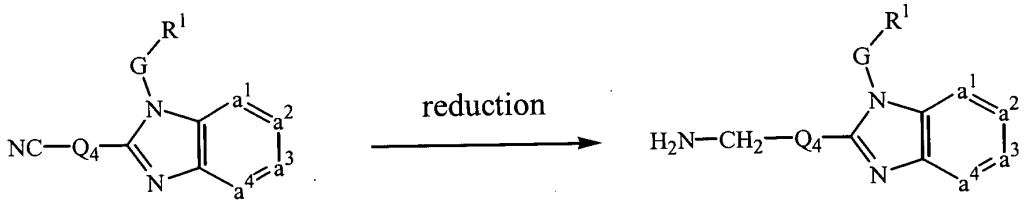


(IX) (I-a-1-2)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and H_2N-Q_3H being defined as Q according to claim 1 provided that both R^6 substituents are hydrogen or R^2 and R^4 are both hydrogen, and the carbon adjacent to the nitrogen carrying the R^6, or R^2 and R^4 substituents contains at least one hydrogen, in the presence of an amination reagent;

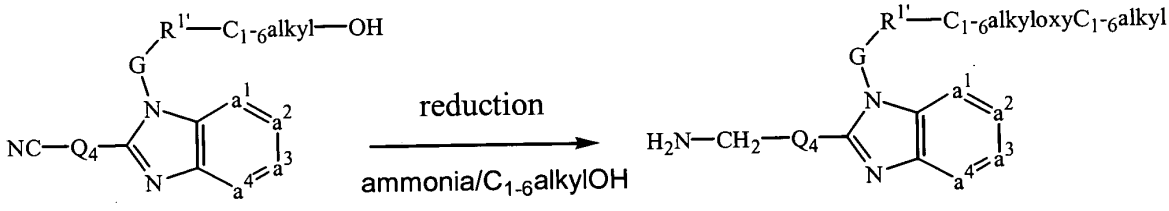
h) reducing an intermediate of formula (X)



(X) (I-a-1-3)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $H_2N-CH_2-Q_4$ being defined as Q according to claim 1 provided that Q comprises a $-CH_2-NH_2$ moiety, in the presence of a reducing agent;

i) reducing an intermediate of formula (X-a)



(X-a) (I-a-1-3-1)

with G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, $H_2N-CH_2-Q_4$ being defined as Q according to claim 1 provided that Q comprises a $-CH_2-NH_2$ moiety, and $R^{1'}$

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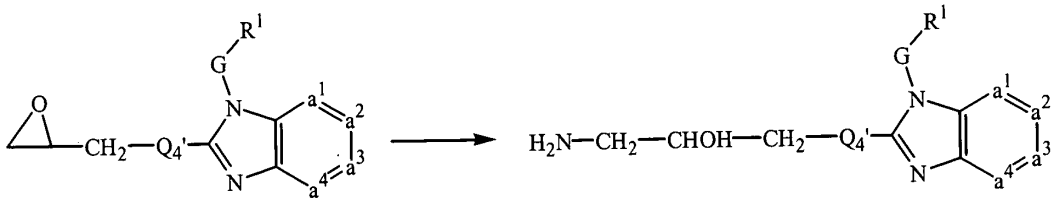
being defined as R^1 according to claim 1 provided that it comprises at least one substituent, in the presence of a reducing agent and solvent;

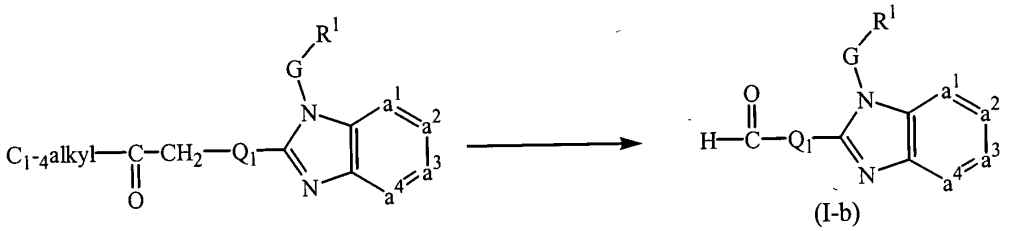
j) amination of an intermediate of formula (XI)



(XI) (I-a-1-3-2)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $H_2N-CH_2-CHOH-CH_2-Q_4$, being defined as Q according to claim 1 provided that Q comprises a $CH_2-CHOH-CH_2-NH_2$ moiety, in the presence of an amination reagent;

k) reacting an intermediate of formula (XII) with formic acid, formamide and ammonia



(XII) (I-b)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $H-C(=O)-Q_1$ being defined as Q according to claim 1 provided that R^2 or at least one R^6 substituent is formyl;

l) amination of an intermediate of formula (XIII) by reaction with an intermediate of formula (XIV)

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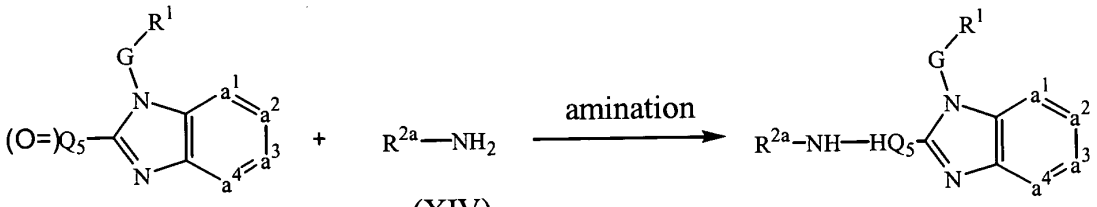
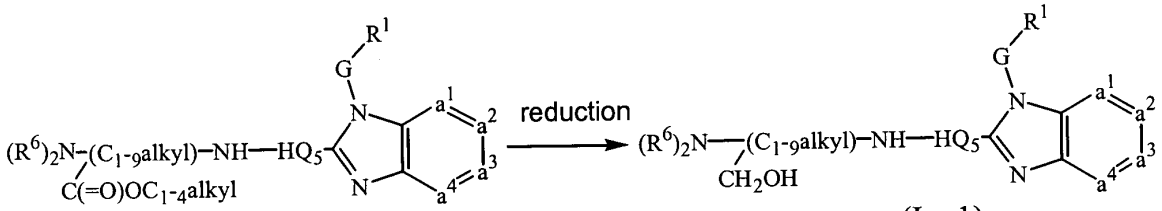


with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and R^{2a}-NH-HQ_5 being defined as Q according to claim 1 provided that R^2 is other than hydrogen and is represented by R^{2a}, R^4 is hydrogen, and the carbon atom adjacent to the nitrogen atom carrying the R^2 and R^4 substituents, carries also at least one hydrogen atom, in the presence of a reducing agent;

m) reducing an intermediate of formula (XV)



with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $(R^6)_2N$-[$(C_{1-9}$alkyl$)CH_2OH$]-NH-HQ_5 being defined as Q according to claim 1 provided that R^2 is other than hydrogen and is represented by C_{1-10}alkyl substituted with $N(R_6)_2$ and with hydroxy, and the carbon atom carrying the hydroxy, carries also two hydrogen atoms, and provided that R^4 is hydrogen, and the carbon atom adjacent to the nitrogen atom carrying the R^2 and R^4 substituents, carries also at least one hydrogen atom, with a reducing agent;

n) deprotecting an intermediate of formula (XVI), (XVI-a) or (XVI-b)

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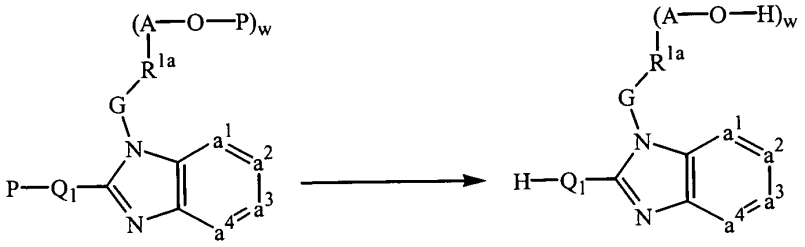
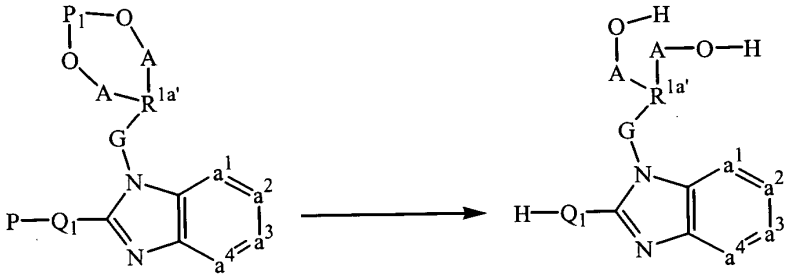
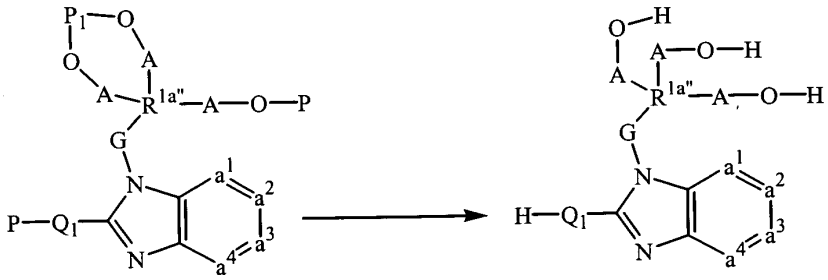


(XVI) (I-d)



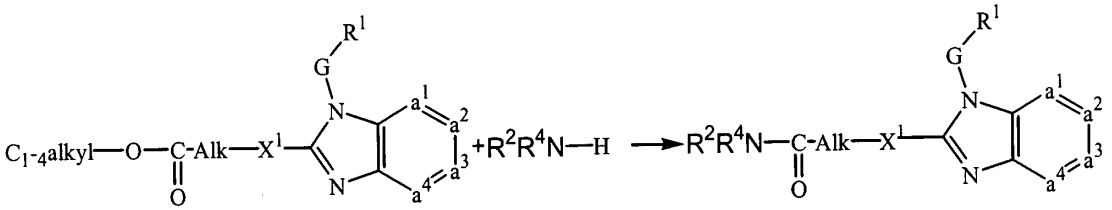
(XVI-a) (I-d-1)



(XVI-b) (I-d-2)

with G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and H-Q_1 being defined as Q according to claim 1 provided that R^2 or at least one R^6 substituent is hydrogen, and R^{1a}-(A-O-H)$_w$, $R^{1a'}$-(A-O-H)$_2$ and $R^{1a''}$-(A-O-H)$_3$ being defined as R^1 according to claim 1 provided that R^1 is substituted with hydroxy, hydroxyC_{1-6}alkyl, or HO(-CH_2-CH_2-O)$_n$-, with w being an integer from 1 to 4 and P or P_1 being a protecting group, with ~~a suitable~~ an acid;

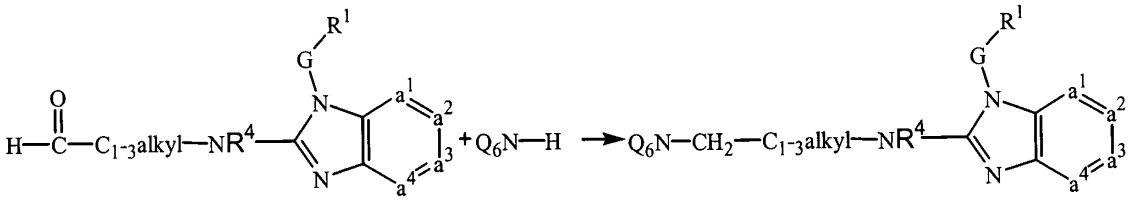
o) amination of an intermediate of formula (XVII)



(XVII) (XVIII) (I-e)

with R^1, G, $-a^1=a^2-a^3=a^4-$, Alk, X^1 R^2 and R^4 defined as in claim 1, in the presence of **an** amination agent;

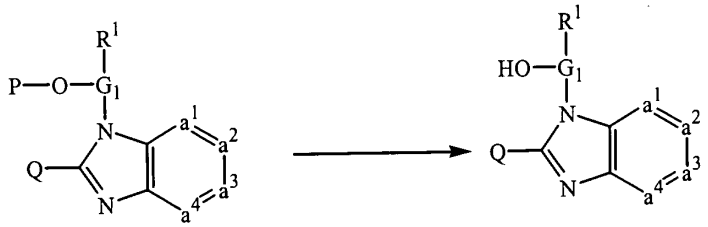
p) amination of an intermediate of formula (XIX)



(XIX) (XX) (I-p)

with R^1, G, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $Q_6N\text{-}CH_2\text{-}C_{1\text{-}3}alkyl\text{-}NR^4$ being defined as Q according to claim 1 provided that in the definition of Q, X^2 is $C_{2\text{-}4}alkyl\text{-}NR^4$, in the presence of an amination agent;

q) deprotecting an intermediate of formula (XXI)

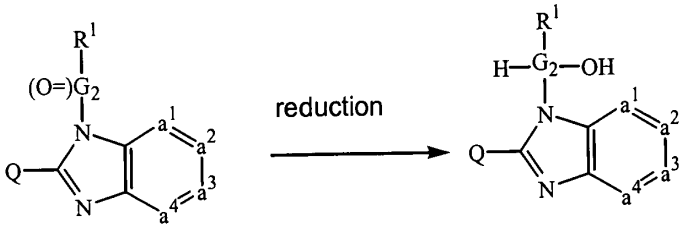


(XXI) (I-q)

with R^1, Q, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $HO\text{-}G_1$ being defined as G according to claim 1 provided that G is substituted with hydroxy or $HO\text{-}(CH_2CH_2O\text{-})_n$; and

r) reducing an intermediate of formula (XXII)

D2



(XXII) (I-q-1)

with R^1, Q, and $-a^1=a^2-a^3=a^4-$ defined as in claim 1, and $H-G_2-OH$ being defined as G according to claim 1 provided that G is substituted with hydroxy and the carbon atom carrying the hydroxy substituent carries also at least one hydrogen, in the presence of a reducing agent.

Claims 16 to 17 ***(cancelled)***

18. ***(previously presented)*** The process of claim 15, further comprising the step of converting compound of formula (I'), stereochemically isomeric forms, metal complexes, quaternary amines or *N*-oxide forms thereof, into a therapeutically active non-toxic acid addition salt by treatment with an acid.

19. ***(previously presented)*** The process of claim 15, further comprising the step of converting compound of formula (I'), stereochemically isomeric forms, metal complexes, quaternary amines or *N*-oxide forms thereof, into a therapeutically active non-toxic base addition salt by treatment with alkali.

20. ***(currently amended)*** The process of claim 15, further comprising the step of converting the acid addition salt form of compound of formula (I')~~,~~ **or** stereochemically isomeric forms, ~~**metal complexes, quaternary amines or *N*-oxide forms**~~ thereof, into the free base by treatment with alkali.

21. ***(currently amended)*** The process of claim 15, further comprising the step of converting the base addition salt form of compound of formula (I')~~,~~ **or** stereochemically isomeric forms, ~~**metal complexes, quaternary amines or *N*-oxide forms**~~ thereof, into the free acid by treatment with acid.

22. ***(currently amended)*** The process of claim 15, further comprising the step of converting said compound of formula (I')~~,~~ **or** stereochemically isomeric form~~, metal complex, quaternary amine or *N*-oxide form thereof~~, into a different form of compound of formula (I'), stereochemically isomeric form, metal complex, quaternary amine or *N*-oxide form thereof.